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FILING DATE: ***February 03, 2003***
RELATED PCT APPLICATION NUMBER: *PCT/US04/03143*

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02/03/03 J105 U.S. PTO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

02/03/03 09C857 U.S. PTO 60/444391

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Yuqiang	Wang	938 November Drive Cupertins, CA 95014

[ ] Additional inventors are being named on the ___ separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

Compounds useful in coating stents to prevent and treat stenosis and restenosis

CORRESPONDENCE ADDRESS

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ENCLOSED APPLICATION PARTS (check all that apply)

[X] Specification Number of Pages 14
[ ] CD(s), Number
[ ] Drawing(s) Number of Sheets
[ ] Other (specify)
[ ] Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

[X] Applicant claims small entity status. See 37 CFR 1.27.
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Respectfully submitted,

SIGNATURE _____ Date 01 30 03

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REGISTRATION NO. (if appropriate)

Docket Number:

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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Arteries that supply blood and oxygen to the heart muscles are called coronary arteries. Coronary artery disease (CAD) occurs when cholesterol plaque (a hard, thick substance comprised of varying amounts of cholesterol, calcium, muscle cells, and connective tissue, which accumulates locally in the artery walls) builds up in the walls of these arteries, a process called arteriosclerosis. Over time, arteriosclerosis causes significant narrowing of one or more coronary arteries. When coronary arteries narrow more than 50 to 70%, the blood supply beyond the plaque becomes inadequate to meet the increased oxygen demand during exercise. Lack of oxygen (ischemia) in the heart muscle causes chest pain (angina) in most patients. However, some 25% of patients experience no chest pain at all despite documented ischemia, or may only develop episodic shortness of breath instead of chest pain. These patients have silent angina and have the same risk of heart attack as those with angina. When arteries are narrowed in excess of 90-99%, patients often have angina at rest (unstable angina). When a blood clot (thrombus) forms on the plaque, the artery may become completely blocked, causing death of a part of the heart muscles (heart attack, or *myocardial infarction).*

Angioplasty (also called percutaneous transluminal coronary angioplasty or PTCA) is a general term used to describe a procedure for treating such blockages and/or blood clots. PTCA can produce excellent results in carefully selected patients who may have one or more severely narrowed artery segments, which are suitable for balloon dilatation, stenting, or atherectomy. During PTCA, a local anesthetic is injected into the skin over the artery in the groin or arm. The artery is punctured with a needle and a plastic sheath is placed into the artery. Under x-ray guidance (fluoroscopy), a long, thin plastic tube, called a guiding catheter, is advanced through the sheath to the origin of the coronary artery from the aorta. A contrast dye containing iodine is injected through the guiding catheter so that x-ray images of the coronary arteries can be obtained. A small diameter guide wire (0.014 inches) is threaded through the coronary artery narrowing or blockage. A balloon catheter is then advanced over the guide wire to the site of the obstruction. This balloon is then inflated for about 1 minute, compressing the plaque and enlarging the opening of the coronary artery. Balloon inflation pressures may vary from as little as one or two atmospheres of pressure, to as much as 20 atmospheres. Finally, the balloon is deflated and removed from the body.

Over the last decade, new devices that can cut out pieces of a plaque, vaporize it with a laser, bore out the blockage with a kind of surgical drill bit, or insert a tiny metal, stent, spring into the coronary artery to help keep it stretched open have been developed. After the coronary artery blockage has been treated by angioplasty, a small, expandable metal scaffold (the stent) is inserted into the artery and expanded. The purpose of the stent is to maintain the opening created by the angioplasty, and prevent a recurrence of the blockage. Intracoronary stents are deployed in either a self-expanding fashion, or most commonly they are delivered over a conventional angioplasty balloon. When the balloon is inflated, the stent is expanded and deployed, and the balloon is removed, the stent remains in place in the artery. Atherectomy devices are inserted into the coronary artery over a standard angioplasty guide wire, and then activated in varying fashion, depending on the device chosen.

There are several reasons to undergo an angioplasty procedure. If chest pain symptoms are not easily controlled with medications, or if symptoms prevent the patient from participating in daily activities, an angioplasty may decrease or eliminate the chest pains. After the procedure,

fewer cardiac medications may be required. If the patient is experiencing chest pains at rest (i.e., without exercise or exertion), or if chest pain continues after a heart attack, an angioplasty procedure is used to treat the blockage causing the problem. One recently completed study found that in certain male patients with chest pains at rest, including those who had suffered a small heart attack, treatment of coronary stenosis with an angioplasty procedure resulted in fewer long-term adverse events than treatment with medications alone.

Long-term benefits of PTCA depend on the maintenance of the newly-opened coronary artery(ies). Recurrent narrowing (restenosis) of a coronary artery by formation of new blockages at the site of the angioplasty or stent occurs within 3-6 months in 40-50% of patients who have angioplasty. This incidence has been reduced to 20-30% with the use of stents. Obviously, whether a stent is used or not restenosis remains a major problem. There are two major mechanisms for restenosis. The first is by thrombosis, or blood clotting, at the site of treatment. The risk of thrombosis is the greatest immediately after angioplasty, because the resultant tissue trauma tends to trigger blood clotting. This form of restenosis is greatly reduced by using anti-clotting drugs for a time during and after the procedure. The second form of restenosis is tissue growth at the site of treatment. This form of restenosis is a proliferation of the endothelial cells that normally line blood vessels tends to occur during the first 3 to 6 months after the procedure, and is not prevented by anti-clotting drugs.

The clotting mechanism is one of the most important and complex of physiologic systems. Blood must flow freely through the blood vessels in order to sustain life. But if a blood vessel is traumatized, the blood must clot to prevent life from flowing away. Thus, the blood must provide a system that can be activated instantaneously – and that can be contained locally – to stop the flow of blood. This system is called the clotting mechanism.

There are two major facets of the clotting mechanism – the platelets, and the thrombin system. The platelets are tiny cellular elements, made in the bone marrow, that travel in the bloodstream waiting for a bleeding problem to develop. When bleeding occurs, chemical reactions change the surface of the platelet to make it "sticky." Sticky platelets are "activated." These activated platelets begin adhering to the wall of the blood vessel at the site of bleeding, and within a few minutes they form what is called a "white clot," a clump of platelets appears white to the naked eye. The thrombin system consists of several blood proteins that, when bleeding occurs, become activated. The activated clotting proteins engage in a cascade of chemical reactions that finally produce a substance called fibrin. Fibrin can be thought of as a long, sticky string. Fibrin strands stick to the exposed vessel wall, clumping together and forming a web-like complex of strands. Red blood cells become caught up in the web, and a "red clot" forms.

A mature blood clot consists of both platelets and fibrin strands. The strands of fibrin bind the platelets together, and "tighten" the clot to make it stable. In arteries, the primary clotting mechanism depends on platelets. In veins, the primary clotting mechanism depends on the thrombin system. But in reality, both platelets and thrombin are involved, to one degree or another, in all blood clotting.

The clotting system, like all complex physiologic systems, can produce problems. Blood clots forming on atherosclerotic plaques in the arteries are the major cause of heart attack and stroke. Blood clots forming in the veins of the legs produce a painful condition called phlebitis, and when these venous blood clots break off ("embolize") they move into the lungs and produce a dangerous condition called pulmonary embolus.

Drugs are used to prevent or treat abnormal blood clotting. These drugs can be aimed either at the platelets, or at the thrombin system.

Drugs aimed at the thrombin system.

A. Drugs that prevent further fibrin from forming. These drugs, which inhibit one or more of the proteins involved in the thrombin clotting system, are used for both arterial and venous clotting problems.

Heparin. Heparin is an intravenous drug that has an immediate (within seconds) inhibitory effect on the thrombin system. Its dosage can be adjusted frequently, following the PTT blood test (the partial thromboplastin time) to achieve the desired effect.

Low molecular weight heparin: enoxaparin, dalteparin. LMWH is a "purified" derivative of heparin. Its major advantages are that it can be given as a skin injection (which almost anyone can learn to do in a few minutes), and does not need to be closely monitored with blood tests. Thus, unlike heparin, LMWH can be administered safely on an outpatient basis.

Coumadin Coumadin is an oral anti-thrombin drug that can be taken chronically. The dose must be carefully monitored by following the prothrombin time (PT), a blood test.

B. Drugs that "dissolve" fibrin – the fibrinolytic drugs. These powerful drugs actually dissolve fibrin strands that have already formed.

TPA, streptokinase, urokinase. These are the intravenous drugs that are administered acutely during the first few hours of an acute heart attack or stroke, to attempt to re-open an occluded artery, and prevent permanent tissue damage.

Drugs aimed at platelets.

These three groups of drugs, in one way or another, reduce the "stickiness" of platelets. They are used most commonly in preventing arterial clots from forming.

Aspirin and diypyramidole. These drugs have a modest effect on platelet "stickiness," but have few important side effects.

Ticlopidine (Ticlid) and clopidrogel (Plavix). These drugs are somewhat more powerful than the first group, but can be poorly tolerated and can have important side effects. They are generally used in patients who need, but cannot tolerate, aspirin.

IIb/IIIa inhibitors: abciximab (Reopro), eptifabitide (Integrilin), tirofiban (Aggrastat). The IIb/IIIa inhibitors are the most powerful group of platelet inhibitors. They inhibit a receptor on the surface of platelets (the so-called IIb/IIIa receptor) that is essential for platelet stickiness. Their chief usage is to prevent acute clotting after interventional procedures (such as angioplasty and stent placement), and in patients with acute coronary artery syndromes, such as unstable angina. These drugs are very expensive and (in general) must be given intravenously.

The most immediate threat of restenosis, especially after stent placement, is thrombosis. For several years, clinical trials have been conducted to devise methods of reducing this form of restenosis. It has now been learned that administering special anti-platelet drugs called IIb/IIIa inhibitors (i.e., the drugs abciximab and eptifabatide) significantly diminish this problem. Thus, tissue growth (i.e., the scar-like) restenosis is the major remaining problem.

Solving tissue growth restenosis has proven to be a tall order. To date, the most effective method of reducing the risk of restenosis has been the use of stents. In fact, the major advantage of stents over angioplasty alone is that with stents the incidence of restenosis has been significantly reduced. However, the risk of restenosis during the first 6 months after a stent remains as high as 20-30%. One of the hottest areas of biomedical research today is in devising stents that inhibit restenosis. The approach with the most immediate promise is to make drug-coated stents. These stents are coated with drugs that inhibit the tissue growth that causes restenosis. Many drugs can inhibit the growth of cells. While many of them would be considered too risky to administer throughout the entire body, the idea of delivering a tiny amount of the drug directly to the tissue that needs to be inhibited is a very attractive one.

Several drug-coated stents are undergoing clinical trials in Europe and the United States right now. The most commonly mentioned are sirolimus-coated stents, rapamycin-coated stents, and paclitaxel-coated stents. In addition, a new technique has been developed to coat stents with a polymer that can deliver DNA to the local tissue. While stent-delivered DNA therapy to inhibit restenosis is farther off than therapy with drug-coated stents, it also has a lot of potential.

The first drug-coated stent has recently been approved for marketing in Europe. The Johnson & Johnson sirolimus-coated stent (brand name: Cypher) was quickly approved after results from the RAVEL trial were presented. The RAVEL trial confirmed the remarkable early finding that there were no instances of restenosis in patients receiving the sirolimus stent. The Cypher stent is currently priced as much as 400% higher than non-coated stents, so cost is a concern to European hospitals and health care systems. But investigators in the RAVEL trial maintain that their data shows that when one factors in the cost savings produced by eliminating restenosis (not to mention the morbidity to the patients that is avoided,) using the drug-coated stent is actually cost-effective.

The results of two large clinical trials using drug-coated stents were recently presented at the Transcatheter Cardiovascular Therapeutics 2002 scientific sessions on Washington D.C. The first of the two trials, the SIRIUS trial, examined the use of the sirolimus-coated stent, from Cordis and Johnson & Johnson. Previous trials with the sirolimus-coated stent suggested a remarkable reduction in restenosis compared to using "bare" metal stents. However, the earlier trials were largely limited to patients whose coronary artery blockages were considered nearly

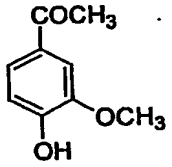
ideal for the use of stents. In the SIRIUS trial, in contrast, patients were intentionally enrolled whose blockages were considered high-risk. Despite this higher risk population of patients, the SIRIUS trial showed a pronounced reduction in the rate of restenosis among patients receiving the sirolimus-coated stents. Patients receiving the drug-coated stent had a 91% reduction in restenosis within the stent itself. The main endpoint of the study, however, was not restenosis but "target vessel failure" defined as cardiac death, heart attack, or the need for revascularization within 9 months of stent placement. The drug-coated stents reduced target vessel failure from 21% to 8.6%. In the second trial, TAXUS II, results with a paclitaxel-coated stent from Boston Scientific were presented. Overall results were comparable to those achieved with the sirolimus-coated stents. In summary, at least two types of drug-coated stents continue to yield remarkable decreases in the rate of restenosis when compared to standard, bare-metal stents.

In this invention, new drugs that can be used to coat stents to prevent or treat restenosis are presented. These new drugs include, but not limited to, the follows:

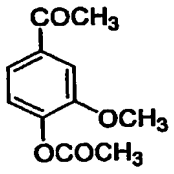
CC-1065 and duocarmycin derivatives, apocynin and derivatives, RGDfV and other RGD peptides, resveratrol and related stilbene compounds, apoptosis inducing factor (ADF), camptothecin class of compounds including the DHA-camptothecin class of drug conjugates, nitroxide-releasing compounds such as the memantine nitrates and other memantine derivatives that incorporate a nitrate or other nitroxide-releasing moiety, DAG-1 peptide.

These drugs may be used alone or in combination with other drugs.

Apocynin and new synthesized derivatives



Apocynin



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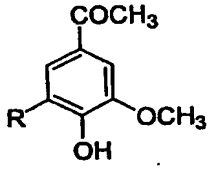

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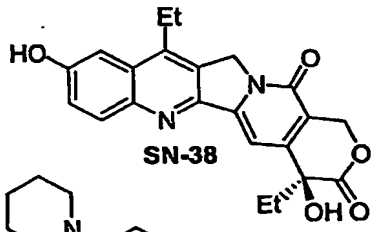

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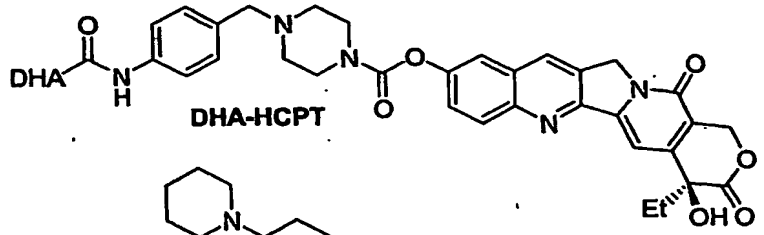

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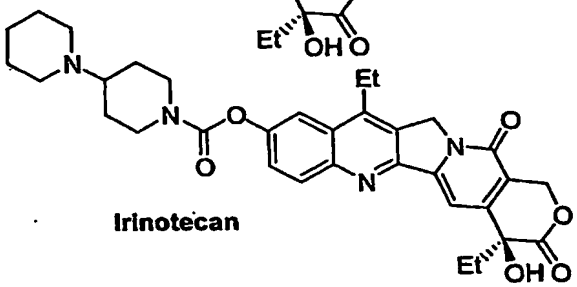

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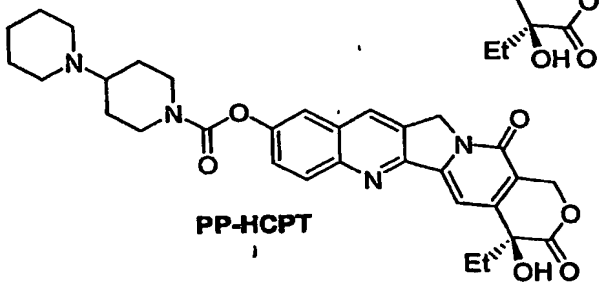
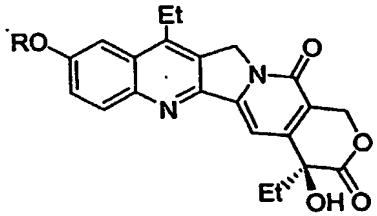


PP-HCPT

New DHA-SN-38 Prodrugs



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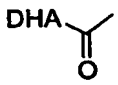

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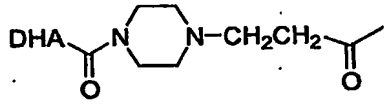

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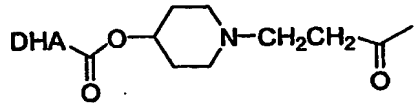

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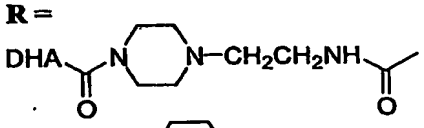

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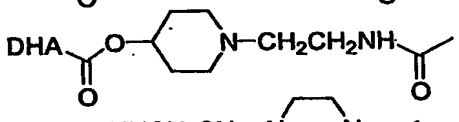

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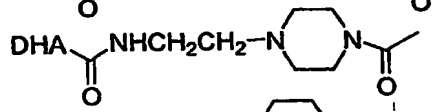

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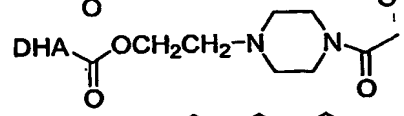

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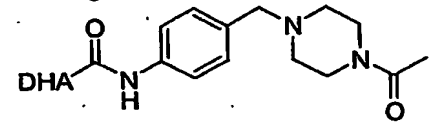

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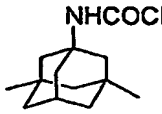
Memantine derivatives



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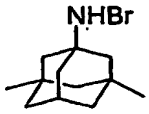

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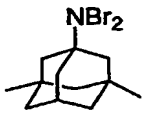

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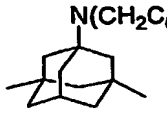

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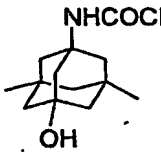

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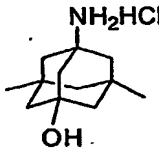

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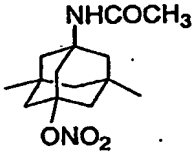

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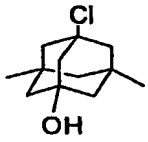

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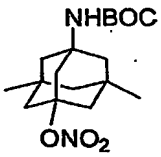

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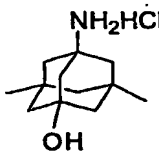

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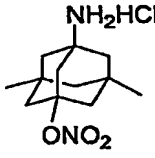

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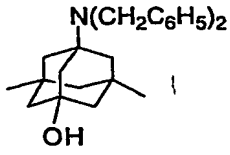

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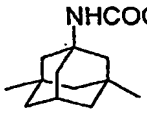

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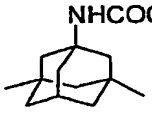

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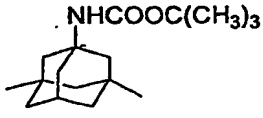

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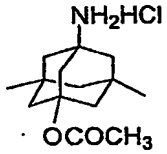

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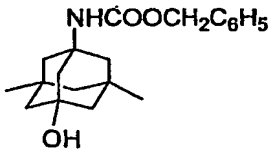

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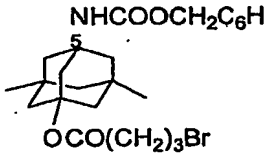

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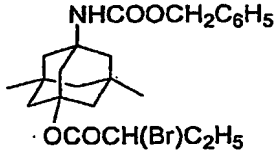

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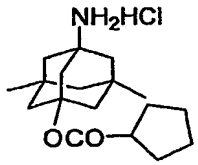

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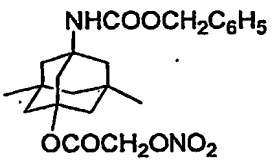

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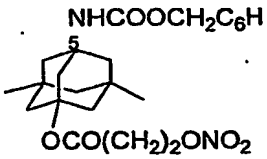

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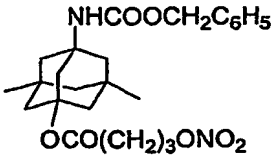

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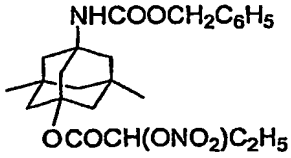

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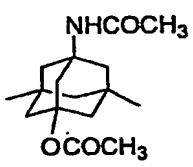

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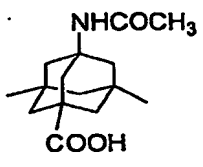

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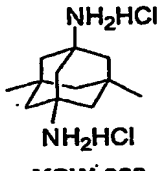

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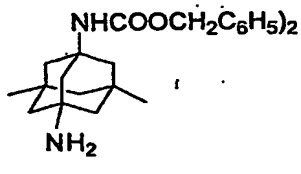

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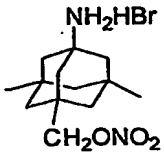

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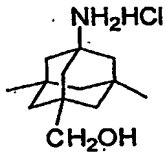

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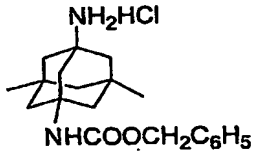

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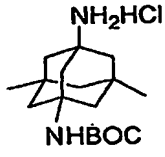

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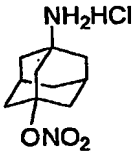

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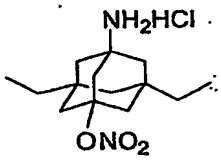

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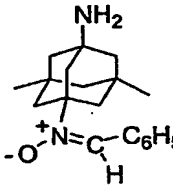

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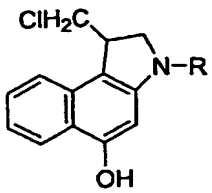

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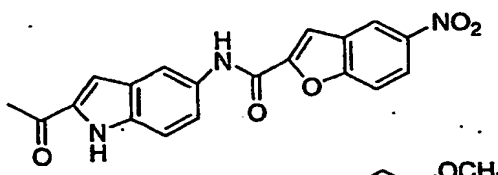
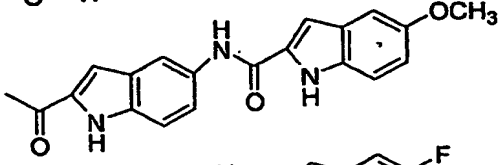
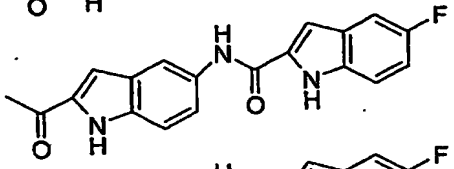
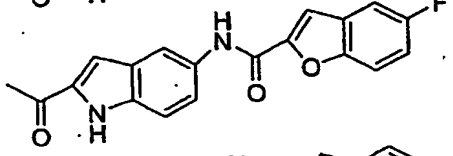
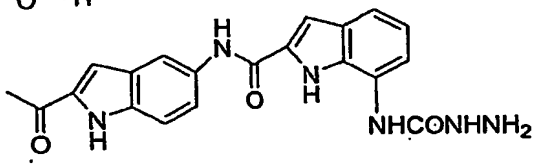
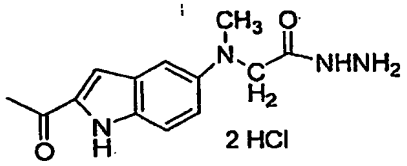
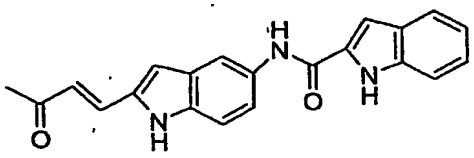
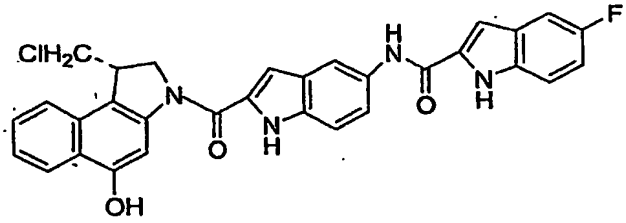
YW-355	580	
YW-366	565	
YW-367	553	
YW-371	553	
YW-373	608	
YW-376	551	
YW-368	549	
YW-380	553	

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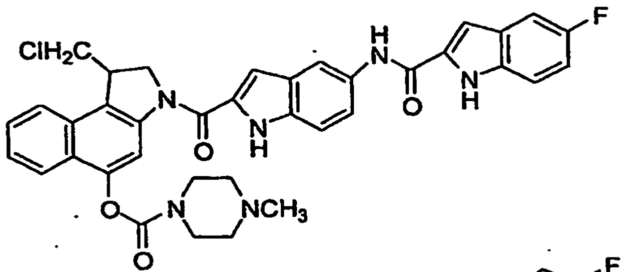

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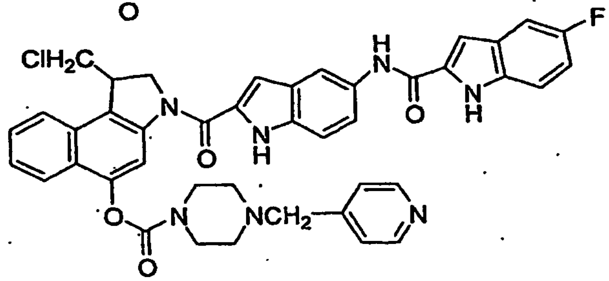

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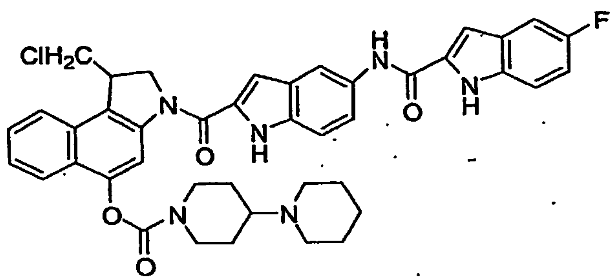

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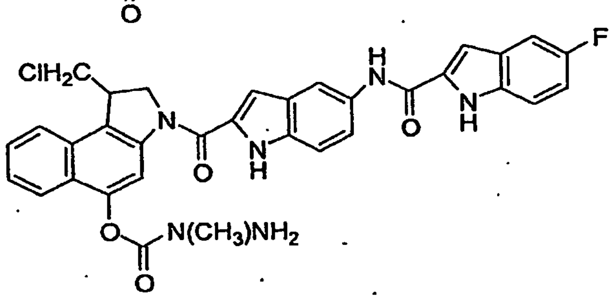

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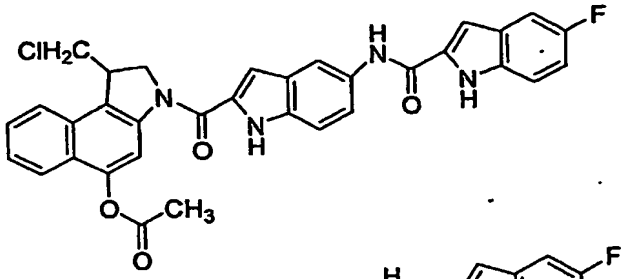
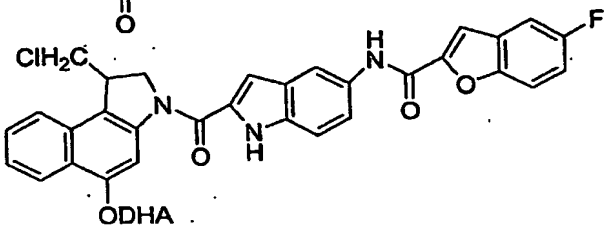
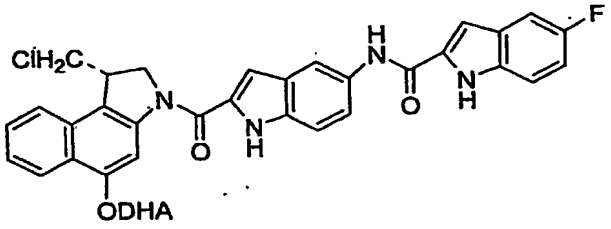
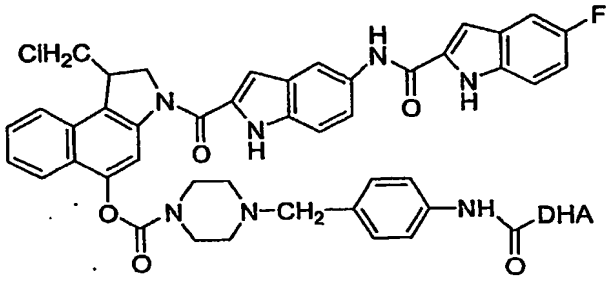
YW-381	595	
YW-372	863	
YW-379	845	
YW-388	1082	

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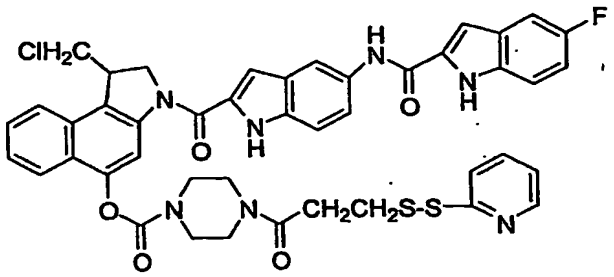
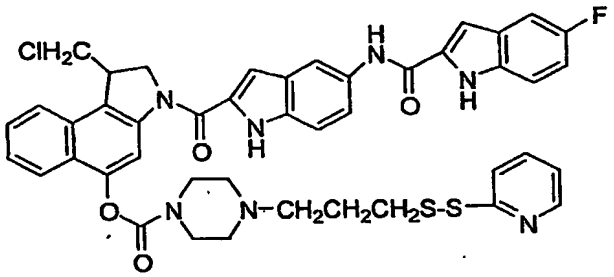
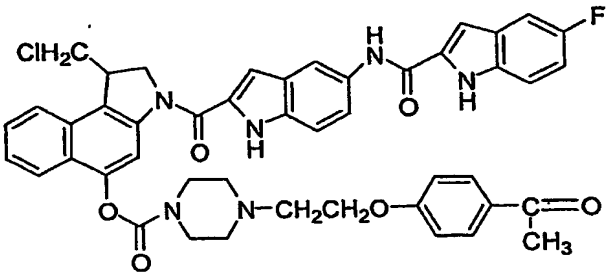
YW-377	862	
YW-378		
YW-382		
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